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| EXAMINER | |
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| ROYDS, LESLIE A | |
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| 1614 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/622,854 | LI, CHIANG J. | |
| | Examiner | Art Unit | |
| | Leslie A. Royds | 1614 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *21 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,4,5,9-17,35,38,39,43-51,53 and 55-74* is/are pending in the application.

4a) Of the above claim(s) *55-72* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,5,9-17,35,38,39,43-51,53,73 and 74* is/are rejected.

7)☒ Claim(s) *1,35,38,39 and 43-51* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

**Claims 1, 4-5, 9-17, 35, 38-39, 43-51, 53 and 55-74 are presented for examination.**

A request for continued examination under 37 C.F.R. 1.114, including the fee set forth in 37 C.F.R. 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R. 1.114, and the fee set forth in 37 C.F.R. 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 C.F.R. 1.114. Applicant's payment and submission filed December 21, 2006 has been received and entered into the present application. Accordingly, prosecution has been reopened.

Claims 1, 4-5, 9-17, 35, 38-39, 43-51, 53 and 55-74 are pending. Claims 1, 4-5, 9-17, 35, 38-39, 43-51, 53 and 73-74 are under examination and claims 55-72 remain withdrawn from consideration pursuant to 37 C.F.R. 1.142(b). Claims 1, 35 and 53 are amended.

Applicant's amendments to the claims and arguments, filed December 21, 2006, have been fully considered. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

### *Objections to the Claims (New Grounds of Objection)*

Claims 1 and 35 are objected to for reciting the phrase "effect the viability of", which is grammatically awkward and should read ---~~effect~~ **affect** the viability of--- for clarity.

Claims 35, 38-39 and 43-51 are objected to under 37 C.F.R. 1.75 as being substantial duplicates of present claims 1, 4-5 and 9-17, respectively. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight different in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. Please reference MPEP §706.03(k). Applicant may wish to consider canceling or amending claims 35,

38-39 and 43-51, since they are drawn to identical subject matter already claimed in present claims 1, 4-5 and 9-17.

***Clai m Rejections - 35 USC § 112, First Paragraph, Written Description Requirement***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-5, 9-17, 35, 38-39, 43-51, 53 and 73-74 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for the reasons of record set forth at pages 2-5 of the previous Office Action dated August 29, 2006, of which said reasons are herein incorporated by reference.

Applicant has amended present claims 1 and 35 to now read upon a method for treating prostate, colon, breast, pancreatic or lung cancer comprising the administration of a G1 and/or S phase checkpoint activator to a subject in need thereof, wherein said checkpoint activator is administered such that expression of a member of the E2F family of transcription factors, selected from the group consisting of E2F-1, E2F-2 and E2F-3, is elevated to selectively activate a checkpoint in cancerous cells, but wherein said checkpoint activator is not toxic to and does not affect the viability of non-cancerous cells in said subject, and further wherein the checkpoint activator is not beta-lapachone. Applicant further relies upon the instant specification at page 34, lines 1-7 and at Table 1 of page 33 in support of this amendment.

Applicant's amendments and traversal of the rejection has been fully and carefully considered, but fails to be persuasive.

Reliance upon the instant disclosure at pages 33-34 in support of this amendment fail to provide adequate written support for the newly amended claim limitation directed to the administration of the checkpoint activator such that "expression of a member of the E2F family of transcription factors,

selected from the group consisting of E2F-1, E2F-2 and E2F-3 is elevated to selectively activate a checkpoint in cancerous cells" (claims 1 and 35). In particular, it is noted that the cited portions of the instant specification upon which Applicant relies are only supportive of the concept of administering the compounds beta-lapachone; 3,4-dihydro-2,2-dimethyl-3-(3-methyl-2-butenyl)-2H-naphtho[1,2-b]pyran-5,6-dione; 3,4-dihydro-2,2-dimethyl-2H-naphtho[1,2-b]thiopyran-5,6-dione; and 3,4-dihydro-4,4-dimethyl-2H-naphtho[1,2-b]thiopyran-5,6-dione to elevate expression of E2F *per se*, but not supportive of the concept of the specific elevation of E2F-1, E2F-2 or E2F-3 using any G1 and/or S phase checkpoint activator compound. This amendment to the claims represents both a narrowing of the concepts presented in the disclosure (i.e., narrowing the disclosed E2F induction to the specific transcription factors E2F-1, E2F-2 or E2F-3) and a broadening of the concepts presented in the disclosure (i.e., broadening the disclosed E2F induction with the specific compounds beta-lapachone; 3,4-dihydro-2,2-dimethyl-3-(3-methyl-2-butenyl)-2H-naphtho[1,2-b]pyran-5,6-dione; 3,4-dihydro-2,2-dimethyl-2H-naphtho[1,2-b]thiopyran-5,6-dione; and 3,4-dihydro-4,4-dimethyl-2H-naphtho[1,2-b]thiopyran-5,6-dione to the entire genus of G1 and/or S phase checkpoint activators), which is clearly demonstrative of the fact that Applicant did not have possession of such concepts at the time of the invention.

For these reasons, and those set forth at pages 2-5 of the previous Office Action of August 29, 2006, rejection of claims 1, 4-5, 9-17, 35, 38-39, 43-51, 53 and 73-74 remains proper and is **maintained**.

***Claim Rejections - 35 USC § 112, First Paragraph, Written Description Requirement***

***(New Grounds of Rejection)***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-5, 10-17, 35, 38-39, 44-51, 53 and 73-74 are rejected under 35 U.S.C. 112, first

paragraph, as failing to comply with the written description requirement. The claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Present claims 1 and 35, and the claims dependent therefrom, are directed to a method for treating prostate, colon, breast, pancreatic or lung cancer comprising the administration of a G1 and/or S-phase checkpoint activator to a subject in need thereof, wherein said checkpoint activator is administered such that expression of a member of the E2F family of transcription factors, selected from the group consisting of E2F-1, E2F-2 and E2F-3, is elevated to selectively activate a checkpoint in cancerous cells, but wherein said checkpoint activator is not toxic to and does not affect the viability of non-cancerous cells in said subject, and further wherein the checkpoint activator is not beta-lapachone. Present claims 73-74 are directed to the same method, wherein the activator to be administered is an orthonapthoquinone.

In particular, the specification as originally filed fails to provide adequate written description for the claim limitations directed to (1) the genus of G1 and/or S phase checkpoint activators (claims 1 and 35) or (2) the genus of orthonapthoquinones as the checkpoint activators (claims 73-74).

Regarding the requirement for adequate written description of chemical entities, Applicant's attention is directed to the MPEP §2163. In particular, *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plain for obtaining the claimed chemical invention." *Eli Lilly*, 119 F.3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for *Examination of Patent Applications* under the 35 U.S.C. 112.1 "Written Description" Requirement ("*Guidelines*"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of

sufficiently detailed, relevant identifying characteristics," including, *inter alia*, "functional characteristics when coupled with a known or disclosed correlation between function and structure..." *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (quoting *Guidelines*, 66 Fed. Reg. at 1106 (emphasis added)). Moreover, although *Eli Lilly* and *Enzo* were decided within the factual context of DNA sequences, this does not preclude extending the reasoning of those cases to chemical structures in general. *Univ. of Rochester v. G.D. Searle & Co.*, 249 Supp. 2d 216, 225 (W.D.N.Y. 2003).

Applicant has failed to provide any structural characteristics, chemical formula, name(s) or physical properties, aside from the express identification of the compounds 3,4-dihydro-2,2-dimethyl-3-(3-methyl-2-butenyl)-2H-naphtho[1,2-b]-pyran-5,6-dione; 3,4-dihydro-2,2-dimethyl-2H-naphtho[1,2-b]-thiopyran-5,6-dione; and 3,4-dihydro-4,4-dimethyl-2H-naphtho[1,2-b]thiopyran-5,6-dione, that would provide adequate written description of the genus of compounds capable of activating a G1 and/or S phase checkpoint that Applicant was actually in possession of, and intended to be used within the context of the present invention, at the time of the present invention.

Applicant's specification states at page 7, lines 1-9, "The cell cycle checkpoint activation modulator can inhibitor cellular proliferation or induce apoptosis. As used herein, a 'modulator' is a molecule which stimulates (i.e. induces) or inhibits cell cycle checkpoint activation. The cell cycle checkpoint activation modulator can be a G1 or S phase checkpoint modulator, or a G1 and S phase checkpoint modulator, a non-peptide or non-protein and can have a molecular weight of less than 5kD. In preferred embodiments, the cell cycle checkpoint activation modulator can be 3,4-dihydro-2,2-dimethyl-3-(3-methyl-2-butenyl)-2H-naphtho-[1,2-b]-pyran-5,6-dione, 3,4-dihydro-2,2-dimethyl-2H-naphtho-[1,2-b]-thiopyran-5,6-dione or 3,4-dihydro-4,4-dimethyl-2H-naphtho-[1,2-b]-thiopyran-5,6-dione."

Such disclosure, while noted, provides only an exemplary and non-limiting teaching of what agents would be considered within the scope of the term "G1 and/or S phase checkpoint activator". Applicant has failed to provide any limiting definition or any chemical or physical characteristics of these

agents such that one of ordinary skill in the art would have been able to readily identify the scope of those compounds encompassed by the term "G1 and/or S phase checkpoint activator".

Though Applicant's claims 73-74 are directed to activators that are "orthonapthoquinone" compounds, the disclosure as originally filed fails to disclose such a genus *per se* for use in the presently claimed method. Further, even if Applicant believes that the three disclosed exemplary checkpoint activators (i.e., 3,4-dihydro-2,2-dimethyl-3-(3-methyl-2-butenyl)-2H-naphtho-[1,2-b]-pyran-5,6-dione, 3,4-dihydro-2,2-dimethyl-2H-naphtho-[1,2-b]-thiopyran-5,6-dione or 3,4-dihydro-4,4-dimethyl-2H-naphtho-[1,2-b]-thiopyran-5,6-dione) are a sufficiently representative set of species to provide adequate written description to now claim the entire genus of orthonapthoquinones, Applicant is reminded that the three exemplified compounds do not address the substantial chemical, structural and, therefore, functional variation that exists among all "orthonapthoquinone" compounds.

In addition, Applicant has also not shown that a common core structural element is, in fact, responsible for its function as a checkpoint activator and, thus, has failed to define the metes and bounds of the claimed genera of "G1 and/or S phase checkpoint activators" or "orthonapthoquinones". MPEP §2163 recites, "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the Applicant was in possession of the claimed genus." Please reference *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

While it is duly noted that the genus of agents capable of functioning as G1 and/or S phase checkpoint activators is limited to those capable of functioning in this manner, it remains that Applicant has not appropriately defined the metes and bounds of the genus, even when limited by function (step-

plus-function form). MPEP §2163 teaches that step-plus-function claims are adequately described if "the written description *adequately links or associates adequately described particular structure*, material, or acts *to the function recited in a step-plus-function claim limitation*," or if "it is clear based on the facts of the application that one skilled in the art would have known what structure, material, or acts perform the function recited in a step-plus-function limitation." The instant application does not meet these criteria. The present specification provides no disclosure beyond the three exemplary agents that would provide a means for identifying compounds, other than those specifically disclosed by Applicant, that would have been amenable for use in the present invention via the identification of a common structural elements that performs the function recited in the claim and would be readily identifiable to one of skill in the art. Furthermore, it has been held that a wish or plan for obtaining the chemical invention as claimed does not provide adequate written description of a chemical invention. Rather, a precise definition, such as by structure, formula, chemical name or physical properties or a combination thereof, is required. Please reference, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004).

While it is recognized that adequate written description of a limitation is not required to be stated *in haec verba* in the specification or claims as originally filed, adequate written support for claim limitations must arise from either an explicit or implicit suggestion by the disclosure to show that such a concept as claimed was actually in possession of Applicant at the time of the invention. For the reasons provided *supra*, Applicant has failed to provide the necessary teachings, by describing the claimed invention with all of its limitations using such descriptive means that fully set forth the claimed invention, in such a way as to reasonably convey to one skilled in the relevant art that Applicant had possession of the (1) the genus of G1 and/or S phase checkpoint activators (claims 1 and 35) or (2) the genus of orthonapthoquinones as the checkpoint activators (claims 73-74).

Accordingly, the claims are considered to lack sufficient written description and are properly

rejected under 35 U.S.C. 112, first paragraph.

***Claim Rejections - 35 USC § 112, First Paragraph, Scope of Enablement***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-5, 9-17, 35, 38-39, 43-51, 53 and 73-74 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the administration of a G1 and/or S phase checkpoint activator selected from 3,4-dihydro-4,4-dimethyl-2H-naptho-[1,2-b]-thiopyran-5,6-dione; 3,4-dihydro-2,2-dimethyl-2H-naptho-[1,2-b]-thiopyran-5,6-dione; 3,4-dihydro-2,2-dimethyl-3-(3-methyl-2-butenyl)-2H-naphto-[1,2-b]-pyran-5,6-dione; or beta-lapachone, for the treatment of prostate, colon, breast, pancreatic or lung cancer in an amount effective to cause tumor regression, does not reasonably provide enablement for the administration of a dose that selectively activates a checkpoint in cancerous cells while elevating the expression of an E2F transcription factor selected from the group consisting of E2F-1, E2F-2 or E2F-3 but not affecting the viability of non-cancerous cells in said subject, for the reasons set forth at pages 5-9 of the previous Office Action dated August 29, 2006, of which said reasons are herein incorporated by reference, and in further view of the following remarks:

Applicant has amended present claims 1 and 35 to now read upon a method for treating prostate, colon, breast, pancreatic or lung cancer comprising the administration of a G1 and/or S phase checkpoint activator to a subject in need thereof, wherein said checkpoint activator is administered such that expression of a member of the E2F family of transcription factors, selected from the group consisting of E2F-1, E2F-2 and E2F-3, is elevated to selectively activate a checkpoint in cancerous cells, but wherein said checkpoint activator is not toxic to and does not affect the viability of non-cancerous cells in said subject, and further wherein the checkpoint activator is not beta-lapachone. Accordingly, the claims are

now readable not only upon the administration of a dose that selectively activates a checkpoint without affecting the viability of non-cancerous cells, but also that the dose is effective to elevate the expression of E2F transcription factors (i.e., E2F-1, E2F-2, E2F-3).

The basis of the rejection set forth at pages 5-9 of the previous Office Action dated August 29, 2006 remains proper despite Applicant's claim amendments because the claims read upon the administration of a dosage amount that is effective to elevate E2F transcription factor expression and also does not affect the viability of non-cancerous cells. However, Applicant has failed to provide any guidance or protocol in the accompanying specification that would be adequate direction to one of ordinary skill in the art at the time of the invention to determine what dosage amounts are effective to achieve the objective of elevated E2F expression with no toxic effect upon non-cancerous cells without placing a burden of undue experimentation upon the skilled artisan in order to determine the dosage amounts capable of functioning in such a manner.

As previously set forth in the Office Action of August 29, 2006, the state of the art at the time of the present invention was such that it recognized the complex nature of treating cancer in general and also the toxic nature of chemotherapeutic therapies, not only to the tumor itself, but also to the normal cells of the body, thus, resulting in numerous adverse side effects. As a result, one of ordinary skill in the art would have had reason to doubt Applicant's allegation that the dosage(s) of checkpoint activator sufficient to selectively activate a checkpoint in cancer cells and thereby induce apoptosis or inhibit cellular proliferation would not have any effect whatsoever on non-cancerous cells because each and every chemotherapeutic regimen available in the art is replete with toxic effects not only on the offending tumor, but also on the body as a whole, due precisely to the fact that the cytotoxic effects of the chemotherapeutic agents cannot be isolated or localized solely to the tumorigenic tissues and cells to be treated absent specific and explicit direction or guidance by Applicant.

It logically follows that the lack of protocol or guidance as to how one of ordinary skill in the art

at the time of the invention would go about determining those dosage amounts of checkpoint activator that are capable of selectively activating a checkpoint while not affecting non-cancerous cells would also equally lack protocol or guidance as to how the skilled artisan would go about determining which of those dosage amounts that are capable of selectively activating a checkpoint while not affecting non-cancerous cells are also effective to elevate the expression of E2F transcription factors (i.e., E2F-1, E2F-2, E2F-3), since Applicant provides no direction to the skilled artisan as to how to determine those dosages capable of selectively activating a checkpoint while not affecting non-cancerous cells, let alone those that are also capable of elevating E2F expression.

In response to the rejection, Applicant states that the claims have been amended to remove the step of determining the appropriate dosage of the checkpoint activating compound and that one of ordinary skill in the art would be able to make and use the invention as claimed and amended herein.

Applicant's amendments and traversal have been fully and carefully considered in their entirety, but fail to be persuasive.

Though Applicant's amendments removing the limitation directed to the determination of the appropriate dosage of the checkpoint activator have been noted, such an amendment does not remedy the fact that Applicant provides no guidance or direction as to the manner and process by which one of ordinary skill in the art would go about determining those dosage amounts of checkpoint activator that are effective to elevate E2F expression but do not affect non-cancerous cells. Accordingly, Applicant's assertion that one would be able to make and use the invention as claimed is clearly not persuasive because the reasons provided above and presented at pages 5-9 of the previous Office Action, as well as the obvious lack of guidance in the accompanying specification, clearly dictate to the contrary.

For these reasons, and those set forth at pages 5-9 of the previous Office Action dated August 29, 2006, rejection of claims 1, 4-5, 9-17, 35, 38-39, 43-51, 53 and 73-74 remains proper and is **maintained**.

*Claim Rejections - 35 USC § 112, Second Paragraph (New Grounds of Rejection)*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4-5, 10-17, 35, 38-39, 44-51, 53 and 73-74 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Present claims 1 and 35, and the claims dependent therefrom, are directed to a method for treating prostate, colon, breast, pancreatic or lung cancer comprising the administration of a G1 and/or S phase checkpoint activator to a subject in need thereof, wherein said checkpoint activator is administered such that expression of a member of the E2F family of transcription factors, selected from the group consisting of E2F-1, E2F-2 and E2F-3, is elevated to selectively activate a checkpoint in cancerous cells, but wherein said checkpoint activator is not toxic to and does not affect the viability of non-cancerous cells in said subject, and further wherein the checkpoint activator is not beta-lapachone.

In particular, Applicant's limitation directed to "a G1 and/or S phase checkpoint activator" does not clearly or deliberately set forth exactly what compounds are to be administered in the context of the claimed method. For example, it is unclear whether the claims are intended to encompass the administration of (1) a compound that is a G1 phase checkpoint activator, (2) a compound that is a S phase checkpoint activator, (3) a compound that is both a G1 and S phase checkpoint activator, or (4) a compound that is a G1 phase checkpoint activator in combination with a separate compound that is an S phase checkpoint activator. In other words, the "and/or" conjunction that is present in the claim does not precisely set forth the metes and bounds of the genus of checkpoint activators intended to be within the scope of the method.

For these reasons, the claims fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and are, thus, properly rejected.

Claims 1, 4-5, 10-17, 35, 38-39, 44-51 and 73-74 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Present claims 1 and 35, and the claims dependent therefrom, are directed to a method for treating prostate, colon, breast, pancreatic or lung cancer comprising the administration of a G1 and/or S phase checkpoint activator to a subject in need thereof, wherein said checkpoint activator is administered such that expression of a member of the E2F family of transcription factors, selected from the group consisting of E2F-1, E2F-2 and E2F-3, is elevated to selectively activate a checkpoint in cancerous cells, but wherein said checkpoint activator is not toxic to and does not affect the viability of non-cancerous cells in said subject, and further wherein the checkpoint activator is not beta-lapachone.

It is noted that the recitation of the limitation "selectively activate a checkpoint in cancerous cells" in inconsistent with the function of the compounds to be administered via the claimed method. In particular, the compounds are G1 and/or S phase checkpoint activators and, thus, activate G1 phase, S phase or both G1 and S phase. In other words, there are limited functions attributed to the claimed activators such that the recitation of activating "a checkpoint" is inconsistent with the claimed G1 and/or S phase activating function of the claimed compounds because it does not specifically refer back to the checkpoints previously recited in the claim. Accordingly, one of ordinary skill in the art at the time of the invention would not have been reasonably apprised of the metes and bounds of the claimed invention because it is not clear whether Applicant intends to active G1 and/or S phase or any other cell cycle checkpoint.

For these reasons, the claims fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and are, thus, properly rejected.

Claims 73-74 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Present claims 1 and 35 are directed to a method for treating prostate, colon, breast, pancreatic or lung cancer comprising the administration of a G1 and/or S phase checkpoint activator to a subject in need thereof, wherein said checkpoint activator is administered such that expression of a member of the E2F family of transcription factors, selected from the group consisting of E2F-1, E2F-2 and E2F-3, is elevated to selectively activate a checkpoint in cancerous cells, but wherein said checkpoint activator is not toxic to and does not affect the viability of non-cancerous cells in said subject, and further wherein the checkpoint activator is not beta-lapachone. Present claims 73-74 are directed to the administration of an orthonapthoquinone.

In particular, there is insufficient antecedent basis for the limitation "said compound" in present claims 73-74, since any reference to such a "compound" is noticeably absent from the claim from which these depend (i.e., claim 1).

For these reasons, the claims fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and are, thus, properly rejected.

***Claim Rejections - 35 USC § 102 (New Grounds of Rejection)***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 4-5, 9-17, 35, 38-39, 43-51, 53 and 73-74 are rejected under 35 U.S.C. 102(a) as being anticipated by Jiang et al. (WO 03/011224; February 2003) in light of Jacob ("Paclitaxel", Pharmacology, 4th Ed., 1996; p.268), cited to show a fact.

Jiang et al. teaches a method for treating mammalian cancers by administering to the patient pharmaceutical compositions (p.5, l.31-33) that contain beta-lapachone or a derivative or analog thereof and a pharmaceutically acceptable solubilizing carrier for use in the treatment of mammalian cancers, such as, e.g., lung, breast, colon, prostate, etc. (p.5, l.1-11), and which may be administered parenterally, preferably intravenously, orally (p.12, l.8-12 and p.22, l.4-26) or topically (p.25, l.20-32). Jiang et al. further teaches that the disclosed pharmaceutical compositions may also contain a second anticancer agent, such as the taxane derivative paclitaxel (p.48, cl.29-32). Figure 12 discloses preferred beta-lapachone analogs and derivatives used in accordance with the teachings of Jiang et al., of which the compound 3-(3-methyl-2-butenyl)-4-methyl-beta-lapachone (i.e., chemically and structurally synonymous with Applicant's claimed compound 3,4-dihydro-2,2-dimethyl-3-(3-methyl-2-butenyl)-2H-naptho-[1,2-b]-pyran-5,6-dione) is expressly identified (bottom row, middle compound).

Jacob is cited for its teaching of paclitaxel as an anticancer agent that effects the formation of stable microtubule bundles, which interferes with late G2 phase, thereby inhibiting cell replication. Please reference Jacob at page 268. Accordingly, paclitaxel as taught by Jiang et al. meets Applicant's limitation of a "microtubule targeting agent" in present claims 16 and 50. In accordance with MPEP §2131.01, it is proper to rely upon a secondary reference for a rejection under 35 U.S.C. 102, provided that the additional reference is relied upon to demonstrate that a characteristic or property not disclosed by the primary reference is, in fact, inherent.

Though Jiang et al. does not expressly teach that the administration of the disclosed beta-lapachone analog compound 3-(3-methyl-2-butenyl)-4-methyl-beta-lapachone inhibits cellular proliferation (claims 4 and 38) or induces apoptosis (claims 5, 39 and 53), the administration of the same compound as claimed [i.e., 3-(3-methyl-2-butenyl)-4-methyl-beta-lapachone, also known as 3,4-dihydro-2,2-dimethyl-3-(3-methyl-2-butenyl)-2H-naptho-[1,2-b]-pyran-5,6-dione] to the same host as claimed (i.e., a patient suffering from prostate, colon, breast, pancreatic or lung cancer) is considered to

necessarily have the same cellular proliferation inhibiting and apoptosis inducing effects in the patient, whether expressly recognized by Jiang et al. or not. Products of identical chemical composition cannot exert mutually exclusive properties when administered under the same circumstances or, in the present case, the same host. Please reference MPEP §2112.

Further, whatever properties or characteristics of the claimed compound [i.e., 3-(3-methyl-2-butenyl)-4-methyl-beta-lapachone, also known as 3,4-dihydro-2,2-dimethyl-3-(3-methyl-2-butenyl)-2H-naptho-[1,2-b]-pyran-5,6-dione] that Applicant has attributed to such a compound, i.e., that it has a molecular weight of less than 5 kD and that it does not damage DNA or stabilize microtubules (claims 1 and 35), are necessarily present in the compound of Jiang et al., absent factual evidence to the contrary, because properties or effects of a compound are not severable from the compound itself, especially when administered under identical conditions.

Applicant's newly amended limitation of part (c) of each of claims 1, 35 and 53 to now read upon the elevated expression of an E2F transcription factor for selectively activating a checkpoint but without toxicity to non-cancerous cells (claims 1 and 35) or for the selective activation of a checkpoint to induce apoptosis but without toxicity to non-cancerous cells (claim 53) is an end-function of the administration of the claimed checkpoint activator compound (i.e., "administered such that") and not an active limiting step of the claimed method. The explanation of the effect obtained when using a compound (i.e., that it selectively activates a checkpoint, elevates expression of E2F transcription factors and does not affect non-cancerous cells) cannot confer novelty on a known process if the skilled artisan was already aware of the occurrence of the desired therapeutic effect. In other words, even if the selective checkpoint activation, E2F transcription factor elevation and lack of effect on non-cancerous cells was not itself recognized as a pharmacological effect of administering the disclosed compound of Jiang et al. for any one of the therapeutic purpose discussed therein, such an effect is not considered a new therapeutic application because a known therapeutic effect and benefit of using this same active agent in the same

host was already known in the prior art. Though mechanisms of action of chemical entities are not doubt important contributions to scientific and pharmaceutical development, the assessment of patentability under 35 U.S.C. 102 is based upon the therapeutic applications and effects of the compounds, not the mechanism by which they exert such a therapeutic effect. Furthermore, it is generally well settled in the courts that a mechanistic property of a chemical compound, or combination of chemical compounds, when administered under identical conditions, is necessarily present, despite the fact that such a mechanistic property may not have been readily apparent to, or recognized by, one of ordinary skill in the art.

*Claim Rejections - 35 USC § 103 (New Grounds of Rejection)*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

**Claims 1, 15-17, 35 and 49-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jiang et al. (WO 03/011224; February 2003) in view of Pardee et al. (WO 00/61142; 2000).**

Jiang et al. teaches a method for treating mammalian cancers by administering to the patient pharmaceutical compositions (p.5, l.31-33) that contain beta-lapachone or a derivative or analog thereof and a pharmaceutically acceptable solubilizing carrier for use in the treatment of mammalian cancers, such as, e.g., lung, breast, colon, prostate, etc. (p.5, l.1-11), and which may be administered parenterally, preferably intravenously, orally (p.12, l.8-12 and p.22, l.4-26) or topically (p.25, l.20-32). Jiang et al. further teaches that the disclosed pharmaceutical compositions may also contain a second anticancer agent, such as the taxane derivative paclitaxel (p.48, cl.29-32). Figure 12 discloses preferred beta-lapachone analogs and derivatives used in accordance with the teachings of Jiang et al., of which the

compound 3-(3-methyl-2-butenyl)-4-methyl-beta-lapachone (i.e., chemically and structurally synonymous with Applicant's claimed compound 3,4-dihydro-2,2-dimethyl-3-(3-methyl-2-butenyl)-2H-naptho-[1,2-b]-pyran-5,6-dione) is expressly identified (bottom row, middle compound).

Though Jiang et al. does not expressly teach that the administration of the disclosed beta-lapachone analog compound 3-(3-methyl-2-butenyl)-4-methyl-beta-lapachone inhibits cellular proliferation (claims 4 and 38) or induces apoptosis (claims 5, 39 and 53), the administration of the same compound as claimed [i.e., 3-(3-methyl-2-butenyl)-4-methyl-beta-lapachone, also known as 3,4-dihydro-2,2-dimethyl-3-(3-methyl-2-butenyl)-2H-naptho-[1,2-b]-pyran-5,6-dione] to the same host as claimed (i.e., a patient suffering from prostate, colon, breast, pancreatic or lung cancer) is considered to necessarily have the same cellular proliferation inhibiting and apoptosis inducing effects in the patient, whether expressly recognized by Jiang et al. or not. Products of identical chemical composition cannot exert mutually exclusive properties when administered under the same circumstances or, in the present case, the same host. Please reference MPEP §2112.

Further, whatever properties or characteristics of the claimed compound [i.e., 3-(3-methyl-2-butenyl)-4-methyl-beta-lapachone, also known as 3,4-dihydro-2,2-dimethyl-3-(3-methyl-2-butenyl)-2H-naptho-[1,2-b]-pyran-5,6-dione] that Applicant has attributed to such a compound, i.e., that it has a molecular weight of less than 5 kD and that it does not damage DNA or stabilize microtubules (claims 1 and 35), are necessarily present in the compound of Jiang et al., absent factual evidence to the contrary, because properties or effects of a compound are not severable from the compound itself, especially when administered under identical conditions.

Applicant's newly amended limitation of part (c) of each of claims 1, 35 and 53 to now read upon the elevated expression of an E2F transcription factor for selectively activating a checkpoint but without toxicity to non-cancerous cells (claims 1 and 35) or for the selective activation of a checkpoint to induce apoptosis but without toxicity to non-cancerous cells (claim 53) is an end-function of the administration

of the claimed checkpoint activator compound (i.e., "administered such that") and not an active limiting step of the claimed method. The explanation of the effect obtained when using a compound (i.e., that it selectively activates a checkpoint, elevates expression of E2F transcription factors and does not affect non-cancerous cells) cannot confer novelty on a known process if the skilled artisan was already aware of the occurrence of the desired therapeutic effect. In other words, even if the selective checkpoint activation, E2F transcription factor elevation and lack of effect on non-cancerous cells was not itself recognized as a pharmacological effect of administering the disclosed compound of Jiang et al. for any one of the therapeutic purpose discussed therein, such an effect is not considered a new therapeutic application because a known therapeutic effect and benefit of using this same active agent in the same host was already known in the prior art. Though mechanisms of action of chemical entities are not doubt important contributions to scientific and pharmaceutical development, the assessment of patentability under 35 U.S.C. 102 is based upon the therapeutic applications and effects of the compounds, not the mechanism by which they exert such a therapeutic effect. Furthermore, it is generally well settled in the courts that a mechanistic property of a chemical compound, or combination of chemical compounds, when administered under identical conditions, is necessarily present, despite the fact that such a mechanistic property may not have been readily apparent to, or recognized by, one of ordinary skill in the art.

Though Jiang et al. does not expressly disclose the use of any one of the variety of chemotherapeutic agents aside from paclitaxel that are presently claimed (see present claims 16-17 and 50-51), Pardee et al. provides teachings of the administration of G1 and/or S phase drugs (i.e., beta-lapachone and derivatives and analogs thereof) in combination with a variety of G2/M phase drugs, such as, e.g., microtubule targeting drugs (taxol, docetaxel, vincristine, vinblastine, nocodazole, epothilones, navelbine, methotrexate) or topoisomerase poisons (teniposide, etoposide, adriamycin, camptothecin, daunorubicin, dactinomycin, mitoxantrone, amsacrine, epirubicin, idarubicin) (p.5, last paragraph and

Table 1 bridging pages 6-7) for the treatment of breast, ovarian, prostate, lung, colon and melanoma cancers (p.11, second paragraph).

One of ordinary skill in the art would have been motivated to combine the beta-lapachone analog 3-(3-methyl-2-butenyl)-4-methyl-beta-lapachone, also known as 3,4-dihydro-2,2-dimethyl-3-(3-methyl-2-butenyl)-2H-naptho-[1,2-b]-pyran-5,6-dione, of Jiang et al. with the microtubule-targeting drugs or topoisomerase poisons of Pardee et al. because Pardee et al. discloses the efficacy of such drugs for the treatment of the cancers (i.e., breast, ovarian, prostate, lung, colon, etc.) when combined with beta-lapachone derivatives or analogs and also because because such compounds were known or recognized in the art to have the same anticancer efficacy in treating cancers such as breast, prostate, colon, lung, etc. The very fact that each was known in the prior art to have the same therapeutic utility raises the reasonable expectation of success that the two compositions, when combined, would have, at minimum, additive, if not synergistic, anticancer efficacy when combined.

As stated in *In re Kerkhoven*, 626 F.2d 846, 205 USPQ 1069, at page 1072 (CCPA 1980): "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose. *In re Susi*, 58 CCPA 1074, 1079-80, 440 F.2d 442, 445, 169 USPQ 423, 426 (1971); *In re Crockett*, 47 CCPA 1018, 1020-21, 279 F.2d 274, 276-77, 126 USPQ 186, 188 (CCPA 1960)."

***Double Patenting***

**Obviousness-Type Double Patenting**

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d

887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

**Provisional Rejections**

Claims 1, 4-5, 9-17, 35, 38-39, 43-51, 53 and 73-74 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims contained within U.S. Patent Application Nos. 10.866,751; 10/887,009; 10/995,565; 11/068,459; 11/069,637; and 11/201,097, each already of record, for the reasons of record set forth at pages 3-5 of the Office Action dated January 17, 2006 and at pages 13-15 of the previous Office Action dated August 29, 2006, of which said reasons are herein incorporated by reference.

Applicant states that they will review these pending applications and will consider filing a Terminal Disclaimer upon notice of allowable subject matter in these applications or in the instant application.

In the absence of any remarks to the contrary or any Terminal Disclaimers, and further in light of the fact that allowable subject matter has not yet been identified in this or any copending application, the present provisional rejections remain proper for the reasons of record and are hereby **maintained**.

**Non-Provisional Rejections (New Grounds of Rejection)**

Claims 1, 4-5, 9-17, 35, 38-39, 43-51, 53 and 73-74 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the method claims of U.S. Patent Nos. 6,245,807; 6,664,288; and 6,875,745. This rejection is directed solely to the claims of the above-cited patents that define methods of use, i.e., the same statutory category of invention.

Due to the number of applicable different patents, and further due to the similarity among the claims of each cited patent, a detailed analysis of why the presently claimed subject matter would have been an obvious variation over each one of the applicable claims in different patents is not presented, but the rejection set forth below is applicable to all of the above-cited patents but for differences in claim numbering.

Claims 1, 4-5, 9-12, 15-17, 35, 38-39, 43-46, 49-51, 53 and 73-74 are rejected over claims 4-5 and 7-14 of U.S. Patent No. 6,875,745. For the following reasons, the presently claimed subject matter would have been obvious not only over such claims but over each of the applicable claims of the remaining U.S. Patents cited above.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claims because the examined claim is either anticipated by, or would have been obvious over, the reference claims.

Although th e conflicting claims are not identical, the claims of the instant application and those of the '745 patent are not considered to be patentably distinct from each other because the present claims clearly render the patented claims obvious.

The present claims clearly provide for the treatment of prostate, colon, breast, pancreatic or lung cancer comprising the administration of a G1 and/or S phase checkpoint activator, i.e., 3,4-dihydro-2,2-dimethyl-3-(3-methyl-2-butenyl)-2H-naptho-[1,2-b]-pyran-5,6-dione, a beta-lapachone derivative, in combination with an additional chemotherapeutic agent, e.g., paclitaxel, vincristine, vinblastine, nocodazole, teniposide, etoposide, adriamycin, camptothecin, daunorubicin, dactinomycin, mitoxantrone, amsacrine, epirubicin, idarubicin, via parenteral or intravenous administration. Though the patented claims are directed to the treatment of a cancerous solid tumor in general using a beta-lapachone or derivative or analog thereof (see present claim 4), claims directed to a species will always anticipate a

genus. Please reference MPEP §2131.02 for a discussion of genus-species situations and also *In re Slayter*, 276 F.2d 408, 411, 125 USPQ 345, 347 (CCPA 1960) and *In re Gosteli*, 872 F.2d 1008, 10 USPQ2d 1614 (Fed. Cir. 1989).

Further, though the patented claims recite specific orders of administration (patented claims 10-11 and 14), one having ordinary skill in the art at the time of the present invention would have found it *prima facie* obvious to alter the schedule of administration in an effort to determine the optimum therapeutic effect. The determination of the optimum order and schedule of administration was a matter well within the purview and skill of the artisan at the time of the invention and would not have required undue experimentation or have been outside the realm of knowledge generally available to the skilled artisan. Factors that would have been taken into consideration when making such a determination would have included, but not been limited to, the age, weight, sex, diet and medical condition of the patient, severity of the disease, route of administration, pharmacological considerations, e.g., activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered as part of a drug combination. Thus, the order and schedule of administration that would have actually been employed would have been expected to vary widely and, in the absence of evidence to the contrary, would not have been inconsistent with that which would have been determined from the instant claims.

Accordingly, rejection of claims 1, 4-5, 9-17, 35, 38-39, 43-51, 53 and 73-74 of the present application is deemed proper over each of the above-indicated patents as claiming obvious and unpatentable variants.

### *Conclusion*

Rejection of claims 1, 4-5, 9-17, 35, 38-39, 43-51, 53 and 73-74 remains proper and is **maintained**.

Claims 55-72 remain **withdrawn** from consideration pursuant to 37 C.F.R. 1.142(b).

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Leslie A. Royds
Patent Examiner
Art Unit 1614

March 9, 2007

Ardin H. Marschel 3/17/07
ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER